IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

THE PROCTER & GAMBLE COMPANY, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	)	Civil Action No. 04-940 (JJF)

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S POST-TRIAL BRIEF

December 20, 2006

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INTRODUCTION

In June, 1985, P&G filed a patent application for a method of treating osteoporosis using certain chemical compounds. One of those compounds was called "2-pyr EHDP." That application issued in due course in 1988 as U.S. Patent 4,761,406 (JTX5), and expired in 2005. In December 1985, while that application was pending, P&G filed a second application claiming the chemical compound 2-pyr EHDP itself. That second application also claimed a nearly identical compound, called "risedronate." P&G's second application, however, did not issue as a patent until the end of 1996, and that patent does not expire until the end of 2013. That patent, U.S. Patent 5,583,122 (JTX1), is in suit here.

In all likelihood, P&G could have obtained the '122 patent years earlier than it did, but doing so would have been pointless. The first several years of the patent's 17-year term would have been wasted because the patent covered the drug product Actonel, which the FDA did not approve until 1998. P&G's election to wait rather than to accept the '122 patent at an earlier date was not illegal or fraudulent, but it did have consequences. The asserted claims of the '122 patent directed to risedronate and its use cover subject matter that would have been obvious in light of the claimed subject matter of the '406 patent. Those claims are therefore invalid for obviousness-type double patenting, because they extend past the expiration of the '406 patent and effectively extend that patent's monopoly.

In addition, P&G has not established an invention date for risedronate before the filing date of the application for the '406 patent. That patent is therefore prior art, and in view of its teachings with respect to 2-pyr EHDP, the asserted claims of the '122 patent are invalid because their subject matter would have been obvious. 35 U.S.C. § 103(a).

NATURE AND STAGE OF THE PROCEEDINGS

P&G markets the pharmaceutical product Actonel for the treatment of diseases of bone metabolism, in particular osteoporosis and Paget's disease. Risedronate is the active ingredient in Actonel. The FDA approved Actonel as a 30 mg daily dose for the treatment of Paget's disease in 1998, and as a 5 mg daily dose and a 35 mg once-weekly dose for the treatment of osteoporosis in 2000 and 2002, respectively. (Joint Statement of Admitted Facts No. 15, D.I.71.)

The '122 patent issued December 10, 1996, and expires December 10, 2013. P&G has listed the '122 patent with the Food & Drug Administration, indicating that it covers the approved dosages and uses of Actonel. Teva USA has filed an Abbreviated New Drug Application seeking approval to market generic equivalents of the Actonel 5 mg, 30 mg and 35 mg dosage forms before the expiration of the '122 patent. Teva USA submitted a certification to the FDA that the '122 patent is invalid, unenforceable or would not be infringed by the commercial manufacture, importation into the United States or sale or use within the United States of Teva USA's proposed commercial risedronate products. On July 2, 2004, Teva USA provided a notice of its certification to P&G in accordance with 21 U.S.C. § 355(j), and P&G brought suit for infringement of the '122 patent in this Court on August 13, 2004. (D.I.1.)

FACTUAL BACKGROUND

I. THE '122 PATENT

P&G filed the '122 patent application on December 6, 1985, in the names of James J. Benedict and Christopher M. Perkins. (JTX1.) The application was a continuation-in-part of U.S. Application Ser. No. 684,543, filed December 21, 1984.[1]

The '122 patent relates to a particular class of compounds called "bisphosphonates" and their use in treating diseases associated with abnormal calcium and phosphate metabolism. The patent refers to wide variety of such diseases including the bone diseases osteoporosis, Paget's disease, and hypercalcemia of malignancy. (JTX1, col.1, ll.26-53.)

The '122 patent includes 23 claims. P&G has asserted claims 4, 16 and 23. Claim 4 is for a chemical compound:

> A disphosphonic acid compound, or pharmaceutically acceptable salt or ester thereof, which is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid.

Claim 16 is for a pharmaceutical composition. Written in independent form, it states:

> A pharmaceutical composition comprising
>
> (a) a geminal diphosphonic acid compound or a pharmaceutically acceptable salt or ester thereof, at a level providing from 0.001 to 600 milligrams of phosphorus in said composition, wherein said diphosphonic acid compound is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid; and
>
> (b) a pharmaceutically acceptable carrier.

Claim 23 defines a method of treatment:

> A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need thereof a safe and effective amount of a composition of claim 16.

[1] P&G has stipulated that the '543 application does not support any of the asserted claims of the '122 patent. (D.I.86.)

(JTX1; DTX309, 311 and 312.) The chemical compound recited in all three asserted claims has the generic name "risedronate." It was referred to internally at P&G as "3-pyr EHDP," and by its compound number "NE-58019." (DTX307; Lenz 93).[2]

II. BISPHOSPHONATES FOR THE TREATMENT OF BONE DISEASES

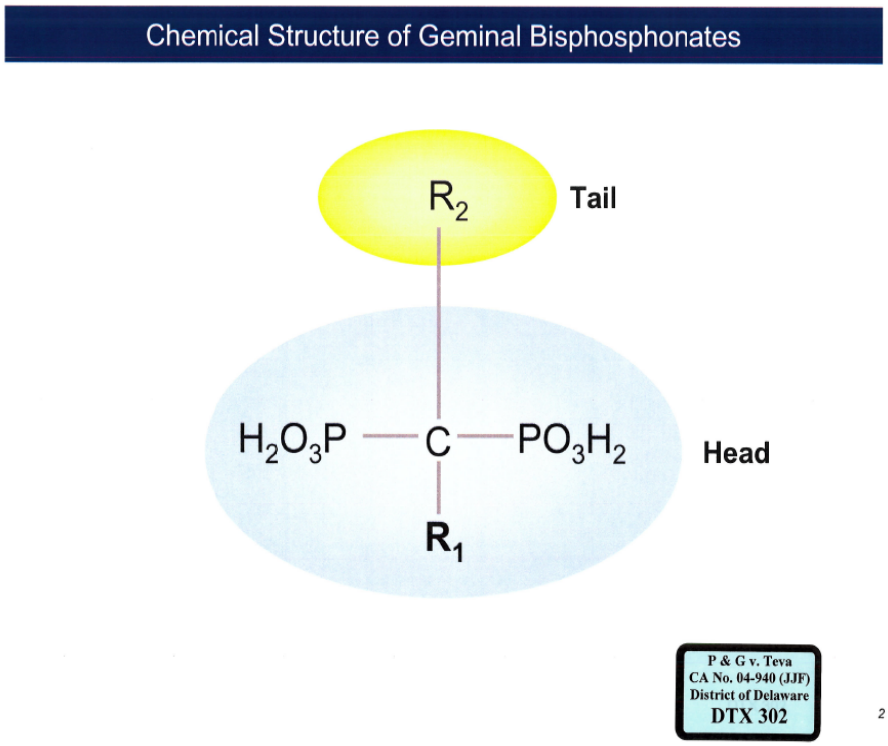
By mid-1985, the earliest invention date that P&G asserts, it was known that bone continuously regenerates itself by a process called "bone remodeling," in which old bone is removed and replaced by new bone. The old bone is removed by cells called osteoclasts and replaced by cells called osteoblasts. Normally, the destruction of bone, called "resorption," and replacement of bone are in balance, but when that balance is disrupted, bone disease results. In the most common bone disease, osteoporosis, bone is destroyed more rapidly than it is replaced, which results in loss of bone. (Bilezikian 352-56; Lenz 84-85.)

By mid-1985, bisphosphonates, also called "diphosphonates," as a class were known to inhibit bone resorption, and therefore to have utility in the treatment of certain bone diseases. (Lenz 68, 85-86.) Bisphosphonate molecules include two phosphonic acid groups. In "geminal" bisphosphonate compounds the phosphonic acid groups are attached to a central carbon atom. The central carbon atom also has two additional groups attached to it. In chemical nomenclature, those groups are known as substituents and are typically labeled R_1 and R_2. (Lenz 69-70; DTX302.)

From a medicinal chemist's viewpoint bisphosphonate molecules have two parts, a "head" and a "tail." The head contains the geminal bisphosphonate portion (the central

[2] Citations to the trial transcript are to the witness's name and the transcript page.

carbon atoms and the phosphonic acid groups) and the R_1 substituent. The tail includes the R_2 substituent. The chemical structure of geminal bisphosphonates showing the head and tail is shown below. (Lenz 71-72.)



The head accounts for the affinity of the molecule for bone. Typically R_1 is a hydroxy (–OH) group. By 1985, persons skilled in the art understood that the head portion should include the hydroxy function. (Lenz 70-71; McKenna 647-48.) The tail, or the R_2 group, is the portion that the medicinal chemist would vary in order to make new compounds. (Lenz 72.)

In mid-1985, the mechanism by which bisphosphonates inhibited bone resorption was not well understood, although it was known that the mechanism included interference with osteoclast function. This "knowledge gap," however, was not a deterrent to research in this area because established biological assays existed to test for

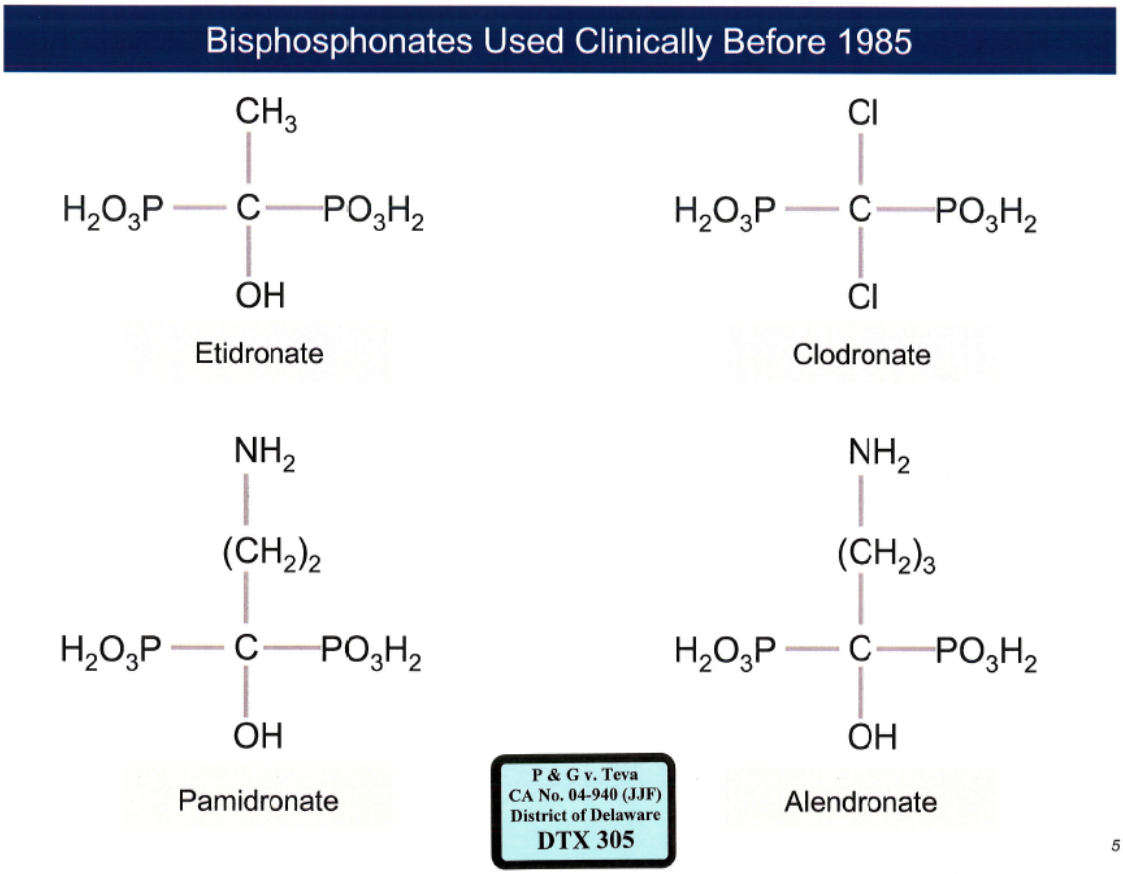
the desired activities. (Bilezikian 404.) In fact, at the time there were many therapeutic areas in which the mechanism of action was not understood on a molecular level, but biological assays to test for the desired activity were available. (Lenz 85-87.)

In addition, in mid-1985, it was also known that in addition to interfering with the cellular process of bone resorption, bisphosphonates could interfere with the mineralization process that occurs during the bone formation phase of the bone remodeling process. This activity is undesirable in particular for compounds targeted for the treatment of osteoporosis. Researchers were therefore looking for compounds that were potent enough to inhibit bone resorption without interfering with bone mineralization. (Lenz 80-81.)

Scientists first began looking at bisphosphonates for the treatment of bone diseases in the 1960's and 70's. The first compound that came out of this research was known as etidronate. Etidronate was clinically tested and ultimately approved for the treatment of Paget's disease, and is still marketed today. (Lenz 79-80; Bilezikian 377.) The chemical name of etidronate is 1-hydroxy-ethane-1,1-disphosphonic acid, often abbreviated EHDP. Etidronate is a geminal bisphosphonate in which R_1 is a hydroxy group and R_2 is a methyl ($-CH_3$) group. (DTX304; Lenz 80.) Although etidronate exhibited significant inhibition of bone resorption, it also inhibited bone mineralization to an undesirable degree, so that the drug was not ideal for the treatment of osteoporosis. Researchers therefore continued to search for additional bisphosphonates that had a profile better suited to the treatment of osteoporosis. (Lenz 80-81.)

By mid-1985, at least three other bisphosphonates had been or were being evaluated clinically for the treatment of osteoporosis: pamidronate, clodronate and

alendronate. Alendronate and pamidronate differ from etidronate and each other only in the composition of the R_2 group. Clodronate differs from all these compounds in that both R groups are chlorine atoms. (Lenz 81-83.) The chemical structures for etidronate, pamidronate, clodronate and alendronate are shown below.



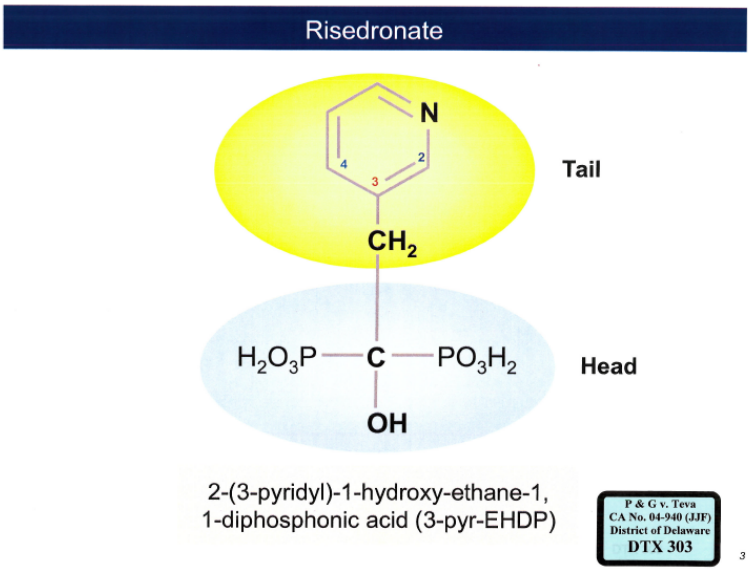
Etidronate, pamidronate and alendronate are all marketed in the United States for the treatment of bone disease. Although clodronate has not been approved for sale in the United States, it is being marketed in Europe for the treatment of bone disease. (Lenz 82.)

Both alendronate and pamidronate include a nitrogen atom in their R_2 groups. Both compounds were known to be potent bone inhibitors of bone resorption, and both

were known to exhibit a low potential for inhibiting bone mineralization. In fact, by mid-1985, bisphosphonates having nitrogen-containing tails in general were known to have a much more pronounced effect on bone resorption in comparison to bone mineralization. Alendronate in particular was found to have an excellent inhibition of bone resorption to inhibition of bone mineralization ratio, with a potency 100 times greater than that of pamidronate. (DTX42 col.13, l.35 – col.14, l.13.)

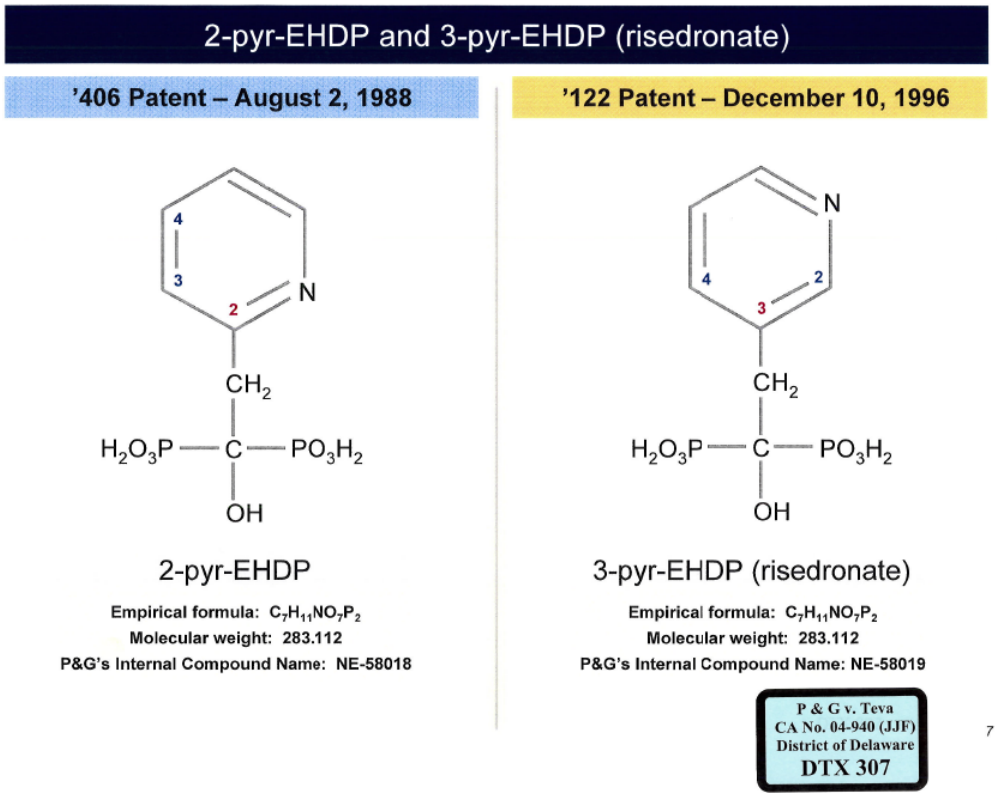
III. RISEDRONATE AND 2-PYR EHDP

The risedronate molecule, claimed in the '122 patent, like the prior bisphosphonates, has a head and a tail portion. The head portion of risedronate is identical to that of etidronate, pamidronate and alendronate, and, as in those compounds, the R_1 group is hydroxy. The tail portion, however, consists of a "pyridine" ring, which is a six-membered ring consisting of five carbon atoms and one nitrogen atom. The risedronate molecule is depicted below:



Although P&G has asserted only claims that are specific to risedronate, other claims of the '122 patent are not restricted to that compound. In particular, the patent also includes claims to a closely related compound, 2-pyr EHDP (also referred to as 2-(2-pyridyl) hydroxyethane-1,1-diphosphonic acid). That compound is covered generically by claims 2 and 3. Pharmaceutical compositions of that compound are covered by claims 12 and 14, and the use of that compound to treat diseases associated with abnormal calcium and phosphate metabolism is covered by claim 21. (JTX1.)

The only difference between the risedronate molecule and that of 2-pyr EHDP is the point of attachment of the pyridyl group to the linking carbon. In 2-pyr EHDP the linking carbon is attached to the pyridyl group at the 2-position. This is why it is known as 2-pyr EHDP, whereas risedronate, in which the pyridyl group is attached to the linking carbon at the 3 position, is known as 3-pyr EHDP. The chemical structures of risedronate and 2-pyr EHDP are shown below.



Risedronate and 2-pyr EHDP are positional isomers. Except for the point of attachment of the bisphosphonate function to the pyridine ring, they are identical. They have the same atomic composition and the same molecular weight. They differ only in the position of the nitrogen atom in the pyridine ring. (Lenz 92.)

IV. PROSECUTION OF THE ASSERTED CLAIMS OF THE '122 PATENT

Although P&G filed the application for the '122 patent in late 1985, that application did not include any claims specific to risedronate, pharmaceutical compositions containing risedronate, or the use of risedronate for treatment of disease. P&G did not present a claim to the compound risedronate (as claimed in asserted claim

4), in application Ser. No. 806,155 ("the '122 patent application") until October 24, 1995, nearly 10 years after filing the application. (JTX2 at 208.)

In addition, P&G did not present a claim either to a pharmaceutical composition containing risedronate (as claimed in claim 16; application claims 70 and 72) or to a method of treatment using a pharmaceutical composition containing risedronate (as claimed in claim 16; application claims 81 and 83) until July 22, 1988, more than three and a half years after filing the application for the '122 patent. (JTX2 at 91.) After P&G had finally presented a claim to a pharmaceutical composition containing risedronate, on October 21, 1988, the examiner stated that the claim (application claim 70) would be allowable if placed in independent form. (JTX2 at 112.) However, P&G did not accept the claim. Instead, on March 24, 1989, P&G canceled the claim and replaced it with another (application claim 108). (JTX2 at 125.) In the same amendment, P&G attempted to provoke an interference with U.S. Patent 4,761,767 ("Bosies"), which claimed other bisphosphonates, not including risedronate. (JTX2 at 134.)

The PTO declared an interference between certain claims of P&G's application and claims of the Bosies patent. None of the counts of the interference covered risedronate, pharmaceutical compositions containing risedronate, or a method of using risedronate. (JTX2 at 171.) In the interference, P&G contended and eventually convinced the PTO that the new claim to the risedronate composition did not correspond to the count. (JTX2 at 134, 152, 192-99.) As a result, that claim could not have been rejected over Bosies, and could have been issued in a patent even while the interference was pending. *See* 37 C.F.R. § 1.615(b):

> Ex parte prosecution as to specified matters may be continued concurrently with the interference with the consent of the administrative patent judge.

See also Manual of Patent Examining Procedure § 2315.01 (5th ed. 1983-1994):

> Where an application involved in an interference includes, in addition to the subject matter of the interference, a separate and divisible invention, prosecution of the second invention may be had during the pendency of the interference by filing a divisional application for the second invention or by filing a divisional application for the subject matter of the interference and moving to substitute the latter application for the application originally involved in the interference.

Despite its success in removing the claims to the risedronate composition from the interference, P&G never prosecuted that claim during the five years that the interference lasted, even though it could have done so.

P&G ultimately lost the interference. (JTX2 at 200-03); *Bosies v. Benedict*, 27 F.3d 539 (Fed. Cir. 1995). However, because the risedronate claims of the application did not correspond to the count of the interference, the PTO allowed them over the Bosies patent and the count. (JTX2 at 112.) Had P&G exercised its right to prosecute claims to risedronate while the interference was pending, those claims would probably have issued long before the '122 patent eventually issued, and would expire long before the '122 patent will actually expire. Of course, not having a patent was no disadvantage – in fact, it exactly dovetailed with P&G's interests. A patent on risedronate whose term was running while risedronate was still in development was a disadvantage, because it meant that the term of protection once the drug was approved would be shorter. P&G timed the issuance well: the patent issued in late 1996, and the first FDA approval for risedronate was shortly thereafter, in early 1998.

V. THE '406 PATENT

The '406 patent, which issued August 2, 1988, is assigned to P&G. It lists Lawrence Flora and Benjamin Floyd as the inventors. Those inventors filed the application for the '406 patent, U.S. Application Serial No. 741,976, on June 6, 1985, six months before Drs. Benedict and Perkins filed the '122 patent application. (JTX5.) The '406 patent includes claims directed to the treatment of osteoporosis by the administration of one of several bisphosphonate compounds, including 2-pyr EHDP. (JTX5, claim 15.)

Although the '122 patent claims 2-pyr EHDP, compositions containing 2-pyr EHDP, and the use of 2-pyr EHDP, the '122 patent application did not reference the application for the '406 patent, which was filed before the '122 patent application and named a different inventive entity. (JTX2.) P&G never brought the application for the '406 patent or the '406 patent itself to the attention of any of the examiners of the '122 patent application during the latter application's eleven-year pendency in the PTO. (JTX2.)

Claim 15 of the '406 patent discloses a method of treating osteoporosis using a dosing regimen in which one of several bisphosphonates (including 2-pyr EHDP) is administered to the patient on a cyclical basis, meaning that treatment periods during which the drug is administered are alternated with rest periods during which no drug is administered. Claim 15 states:

> 15. A method according to claim 1 wherein the bone resorption inhibiting polyphosphonates, and daily dosage ranges, are selected from the group consisting of:
>
> Ethane-1-hydroxy-1,1-diphosphonic acid: from about 0.25 mg P/kg to about 4 mg P/kg;

> Dichloromethane diphosphonic acid: from about 0.12 mg P/kg to about 5 mg P/kg;
>
> Propane-3-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> Butane-4-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> Hexane-6-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> 2-(2-pyridyl-ethane-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> *[2-pyr EHDP]: from about 0.00025 mg P/kg to about 0.01 mg P/kg;* [3] and/or
>
> Hexahydroindan-2,2-diphosphonic acid: from about 0.25 mg P/kg to about 10 mg P/kg;
>
> and their pharmaceutically-acceptable salts and esters.

(JTX5; emphasis added.) Of all the compounds listed in claim 15, 2-pyr EHDP has the lowest recommended dosage strength, i.e., from 0.00025 mg P/kg to about 0.01 mg P/kg. Thus, the claim identifies 2-pyr EHDP as the most potent of all the compounds in the list. (McKenna 683-84; Lenz 88-90.) Claim 15 depends from claim 1, which reads:

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[3] Measuring dosage strengths of bisphosphonates in milligrams of phosphorus allows comparison between two bisphosphonates of different molecular weights. Since each bisphosphonate, by definition, has two phosphonate groups, each has two phosphorus atoms. Thus, referencing the amount of phosphorus in the dose permits a comparison of a number of molecules in the dose rather then its weight. For example, 1mg of etidronate would represent many more bisphosphonate molecules than 1mg of alendronate, because alendronate has a higher molecular weight. But, a 1 mg P dose of etidronate will have the same number of molecules as 1 mg P dose of alendronate. The usefulness of this measure is that it treats two bisphosphonates equally with respect to the number of molecules actually administered. The unit "mg P/kg" represents the number of milligrams of phosphorus of a bisphosphonate per kilogram of body weight. Expressing the dose in this manner allows for it to be adjusted based on the weight of the human or animal being treated.

> 1. A method for treating osteoporosis, in humans or lower animals afflicted with or at risk to osteoporosis, comprising administering to said human or lower animal an *effective amount* of a bone resorption inhibiting polyphosphonate according to the following schedule:
>
> (a) a period of from about 1 day to about 90 days during which said bone resorption inhibiting polyphosphonate is administered daily in a *limited amount*; followed by
>
> (b) a rest period of from about 50 days to about 120 days; and
>
> (c) repeating (a) and (b) two or more times where a net increase in bone mass said human or animal results.

(JTX5; emphasis added).

VI. THE LEVEL OF ORDINARY SKILL IN THE ART

The '122 patent is directed primarily to chemical compositions that can be used to treat diseases of bone metabolism, such as osteoporosis and Paget's disease. (Lenz 68, 74.) The relevant art for the '122 patent is the art of medicinal chemistry and drug discovery, and in the mid-1980s, a person skilled in that art had a Ph.D. in organic chemistry and several years experience in the field. (Lenz 77-78.) Persons skilled in the art would also have experience working with heterocyclic compounds, of which pyridine is an example. (Lenz 73.) Such persons would also have experience in interpreting biological activity and toxicity data for compounds with which they were involved. (Lenz 59, 78-79.)

Dr. George Lenz, Teva USA's expert witness, has a Ph.D. degree in organic chemistry from the University of Chicago, which he obtained in 1967. He did post-doctoral research work at Yale University from 1967 to 1969. He worked in drug discovery for most of his professional career. (DTX134.) In the mid-1980s, Dr. Lenz was working in drug discovery at G.D. Searle, and had been working in the field for 15

years. His experience included a variety of therapeutic areas, including cardiovascular, gastrointestinal, and central nervous system diseases. (Lenz 57-58.)

The person of ordinary skill would not have required special training in organophosphorus chemistry. By 1985, organophosphorus chemistry was a well-developed field, and the synthesis of geminal bisphosphonate compounds was disclosed in the technical literature. The chemistry of the compounds was well understood, and such compounds were straightforward to make. A simple, "one-pot" synthesis for such compounds was described in the literature, and the starting materials could be purchased from chemical suppliers. (DTX76; Lenz 109-111; Benedict 512.) When Dr. Benedict first made risedronate, he employed that procedure. (DTX150 at PG45560.)

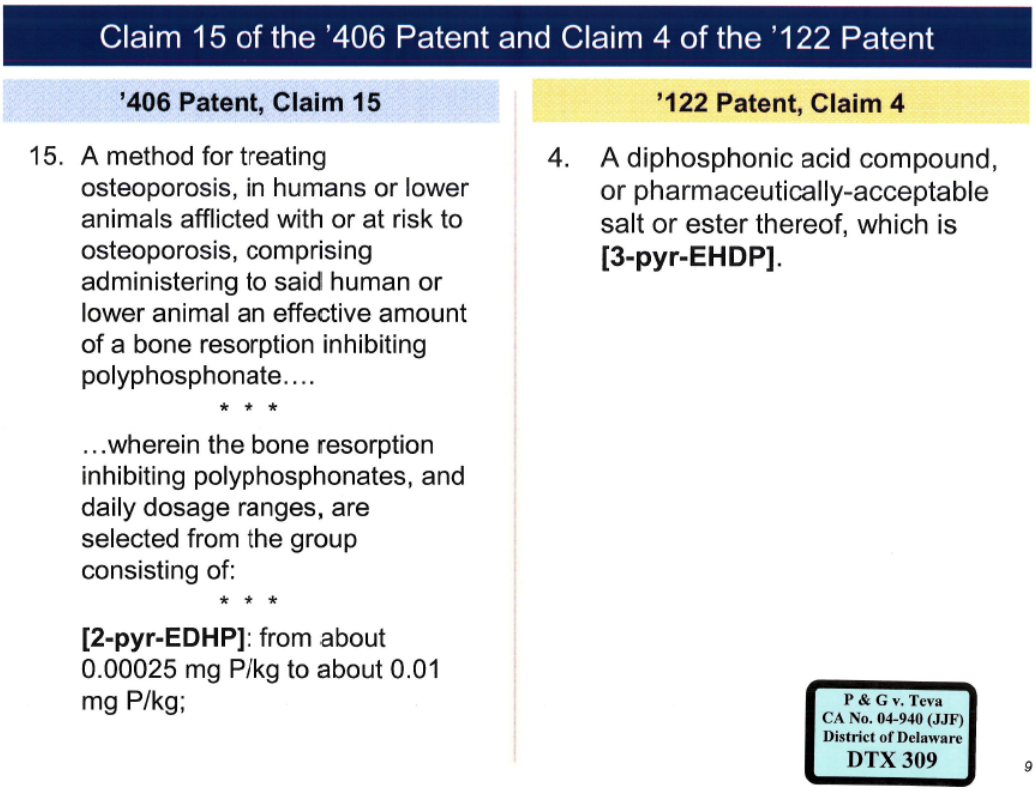
In fact, persons skilled in the art beginning an investigation of a therapeutic class of drugs often had not worked with those drugs before they began a new project. They typically educated themselves about the drugs by reading the technical literature. (Lenz 58-59.) For example, Dr. Lenz carried out a project involving new synthetic routes to certain steroid drugs, and was successful even though he had not previously worked with that class of compounds. (Lenz 53-56.)

Unlike Dr. Lenz, who had 15 years of drug discovery experience as of the mid-1980's, Dr. McKenna, P&G's chemistry expert, was not involved in drug discovery of any kind at that time. Specifically, in the mid-1980s Dr. McKenna was not working on discovering new drugs for treatment of bone disease, nor was he making new bisphosphonates for any pharmaceutical purpose. His publication list does not include any papers on new chemical compounds for pharmaceutical use prior to 1985. (McKenna 639-46.)

VII. DIFFERENCES BETWEEN THE CLAIMED INVENTION OF THE '122 PATENT AND THE CLAIMED INVENTION OF THE '406 PATENT

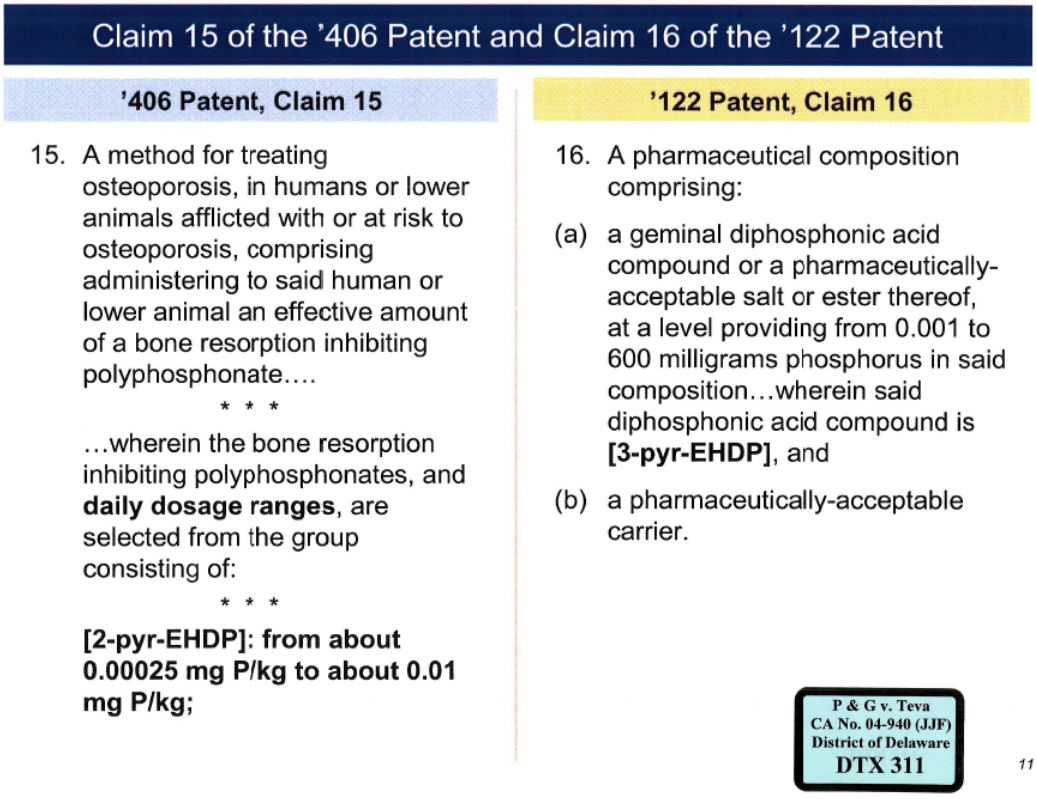
A. The Difference between the Claimed Invention of the '406 Patent and the Asserted Claims is the Difference between Risedronate vs. 2-pyr EHDP

Claim 4 of the '122 patent is a compound claim specific to risedronate. Claim 15 of the '406 patent claims a method of administering several bisphosphonates, including 2-pyr EHDP. The only difference between risedronate and 2-pyr EHDP is the position of the nitrogen in the pyridine ring. The comparison of claim 15 of the '406 patent and claim 4 of the '122 patent is set forth below:



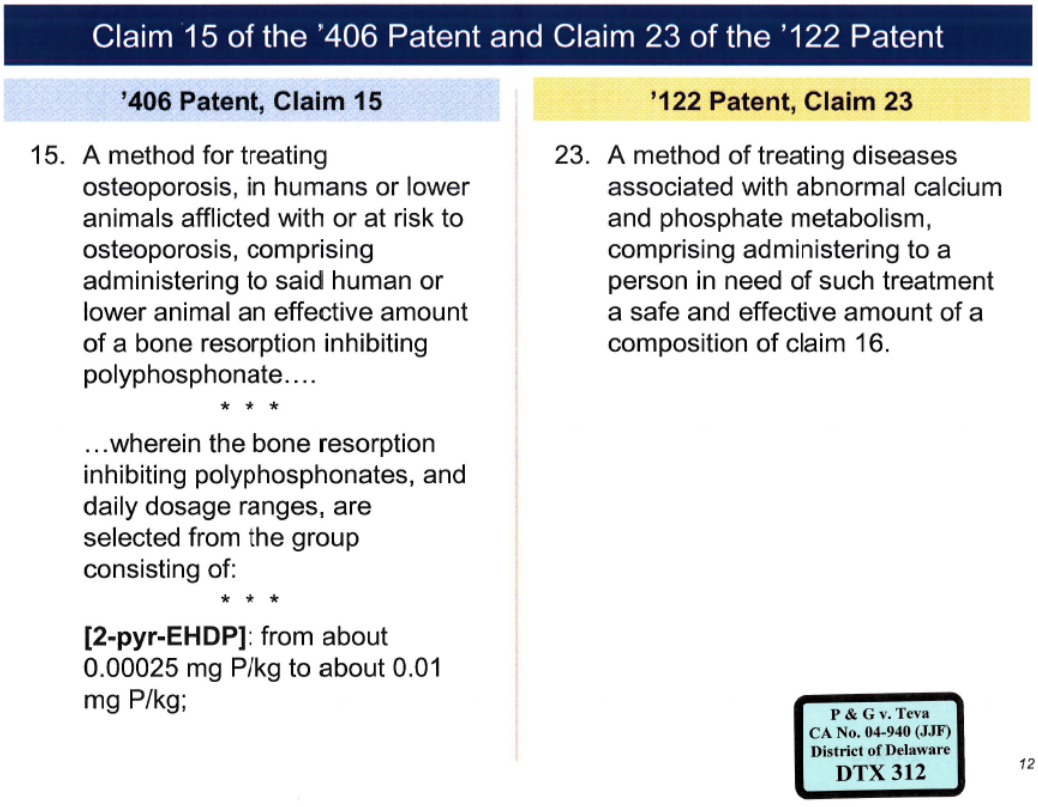
Claim 16 of the '122 patent claims a pharmaceutical composition containing risedronate in an amount from 0.001 to 600 mg of phosphorous and a pharmaceutically

acceptable carrier. Claim 15 of the '406 patent claims the administration of 2-pyr EHDP for the treatment of osteoporosis. One of ordinary skill in the art would understand that the administration would be accomplished using a pharmaceutical composition. (Lenz 113-14.) Furthermore, the dosage range in Claim 15 of the '406 patent falls within the dosage range required by claim 16 of the '122 patent. Thus, the only element of claim 16 of the '122 patent that is not within claim 15 of the '406 patent is the substitution of risedronate for 2-pyr EHDP, and the only difference between risedronate and 2-pyr EHDP is the position of the nitrogen in the pyridine ring. A comparison of those two claims is set forth below:



Claim 23 of the '122 patent claims a method of treating diseases associated with abnormal calcium and phosphate metabolism by administering to a person in need thereof

an effective amount of the composition of claim 16. Claim 15 of the '406 patent claims a method of treating osteoporosis, which is a disease associated with abnormal calcium metabolism. (Lenz 116-17). Thus the only element of claim 23 of '122 patent that is not within claim 15 of the '406 patent is the substitution of risedronate for 2-pyr EHDP, and the only difference between risedronate and 2-pyr EHDP is the position of the nitrogen in the pyridine ring. A comparison of those claims is set forth below:



In short, a comparison between the claims makes clear that the only significant difference between claims 4, 16 and 23 of the '122 patent and the prior art is the substitution of risedronate for 2-pyr EHDP, and that the only difference between those two molecules is the position of the nitrogen on the pyridine ring.

In addition to the claimed invention of claim 15 discussed above, the '406 patent includes additional information about 2-pyr EHDP and eight other bisphosphonate compounds. Those compounds include the known bisphosphonates etidronate ("EHDP"), clodronate ("Cl_2MDP"), pamidronate ("APD"), and alendronate ("ABDP"). The '406 patent provides potency assay results that show that 2-pyr EHDP is the most potent of the eight compounds in inhibiting bone resorption, and that it is effective at a dose 10 times lower (in one animal model) and 100 times lower (in another animal model) than the lowest dose at which any of the other compounds was found to be effective. (JTX5, Tables I and II; Lenz 285-86; Miller 935-36.) In addition, the data in the specification also show that 2-pyr EHDP did not cause a statistically significant inhibition of bone mineralization at the highest dose level at which the assay was conducted. (JTX5, Table III.)

ARGUMENT

I. THE ASSERTED CLAIMS OF THE '122 PATENT ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

The double patenting doctrine precludes a single entity from extending its patent monopoly by obtaining more than one valid patent on either the "same invention," or an "obvious modification of the same invention." *See In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). "Same invention" double patenting, also known as statutory double patenting, is premised on 35 U.S.C. § 101, which states that the inventor of a new product or process may obtain "*a* patent therefor." *See* 3A DONALD S. CHISUM, CHISUM ON PATENTS § 9.02 (2005). Because of this statutory mandate, if the claims of two patents

owned by the same entity cover "identical subject matter," the second to issue is invalid. *See In re Vogel*, 422 F.2d 438, 441 (C.C.P.A. 1970).

Obviousness-type double patenting, in contrast to statutory double patenting, is a judicially created doctrine grounded in public policy. It was created to prevent a patent owner from extending its patent monopoly by claiming, in a later patent, subject matter that is obvious from subject matter that it had already claimed. *Longi*, 759 F.2d at 892. Fundamental to this doctrine is the policy that "the public should . . . be able to act on the assumption that upon the *expiration* of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made." *Id.* at 892-893 (quoting *In re Zickendraht*, 319 F.2d 225, 227-28 (C.C.P.A. 1963)). Thus, obviousness-type double patenting does not require that the two patents claim "identical subject matter," but will invalidate a claim "when it is merely an obvious variation of an invention disclosed and claimed in an earlier patent by the same inventor." *Georgia-Pacific Corp. v. U. S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999).

A. Obviousness-Type Double Patenting Standard

An obviousness-type double patenting analysis involves two steps: "First, as a matter of law the court construes the claim in the earlier patent and the claim in the later patent and construes the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (citing *Georgia-Pacific*, 195 F.3d at 1326-27). Two claims are not "patentably distinct" if the later claim would have been obvious to a person of ordinary skill in the art based on the

earlier claim, in light of the prior art.[4] *See Longi*, 759 F.2d at 893. In other words, if the later claim is encompassed or anticipated by the earlier claim, or is merely an obvious variation of the earlier claim, even if the claims are mutually exclusive, then the later claim is not patentably distinct from the earlier claim and invalid for obviousness-type double patenting. *See Barr*, 251 F.3d at 968; *In re Braithwaite*, 379 F.2d 594, 600-01 (C.C.P.A. 1967). Moreover, modifying an earlier claim by including multiple obvious variations does not add up to a patentable distinction. *See In re Lonardo*, 119 F.3d 960, 967 (Fed. Cir. 1997).

The standard used to determine whether a later claim is an obvious variant of an earlier one is analogous to the standard used to determine obviousness under 35 U.S.C. § 103 as is set out in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). This obviousness analysis applies to patents for any subject matter, including chemical compounds and their uses. Because the analysis implicates "obviousness" and not necessarily "anticipation," it includes no requirement that the claims "overlap," or that the claim of the second patent actually extend the literal scope of the first. *See, e.g.*, *Longi*, 759 F.2d at 896; *In re Zickendraht*, 319 F.2d 225, 227-28 (C.C.P.A. 1963). In *Longi*, claims to nitrogen-containing titanium catalysts supported on magnesium dihalide were held

[4] This is referred to as a one-way test because it only assesses whether the claims of the later patent or application are obvious in view of those of the earlier patent. However, occasionally, an inventor submits two applications and the first filed patent issues later than the patent filed later (first-in, last-out). In such a situation, if the PTO is solely responsible for the delay in the issuance of the first application, a court will apply a two-way test to determine whether a patent is invalid for double patenting. *See, e.g., In re Berg*, 140 F.3d 1428, 1437 (Fed. Cir. 1998); *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991). Under the two-way test, double patenting requires not only that the invention of the second patent have been obvious from that of the first, but also that the first invention have been obvious from the second. *Braat*, 937 F.2d at 589. The two-way test is reserved for that unique sequence of events in the PTO, and does not apply to this case.

unpatentable for obviousness-type double patenting based on claims in an earlier patent covering highly active titanium trihalides, titanium tetrahalide, and titanium oxyhalide catalysts supported on magnesium dihalide. That is, the later claims were unpatentable even though they did not overlap, and in fact were mutually exclusive of, the earlier claims. Similarly, in *Zickendraht*, claims for metallized azo-dyestuff compounds having an unsubstituted benzene ring were unpatentable for obviousness-type double patenting in view of a claim in an earlier patent covering metallized azo-dyestuffs with a substituted benzene ring. Again, the later claims were unpatentable notwithstanding that they did not overlap, and therefore did not literally extend, the claims of the earlier patent.

Although the double patenting analysis is similar to an obviousness determination under section 103, it is different in three respects. First, the claim at issue is not compared to the prior art, but to the claim in the prior patent in light of the prior art. *See In re Boylan*, 392 F.2d 1017, 1018 n.1 (C.C.P.A 1968). The specification of the prior art patent may be used to interpret the language of the claim or claims at issue, but it may not be used as prior art. *See Vogel*, 422 F.3d at 438. Second, the obviousness-type double patenting analysis does not require inquiry into the objective criteria suggesting non-obviousness, as is required by the section 103 obviousness analysis. *Geneva Pharms., Inc. v. GlaxoSmithKline*, 349 F.3d 1373, 1378 n.1 (Fed. Cir. 2003). Third, obviousness-type double patenting does not require inquiry into a motivation to modify the prior art, a factor typically considered as part of the section 103 obviousness analysis. *Id*.

B. Construction of the Claims

1. Claim 15 of the '406 Patent

Claim 15 of the '406 patent is straightforward. It covers a dosing regimen for the treatment of osteoporosis. It sets forth a "Markush group" of eight compounds, each of which can be used in the claimed regimen, together with a daily dosage range for each. In particular, it specifies that one of the compounds is 2-pyr EHDP, and that the dosage range is between 0.00025 mg P/kg and 0.01 mg P/kg. (JTX 5, col.18, ll.32-52.)

2. The Asserted Claims of the '122 Patent

Of the 23 claims in the '122 patent, P&G only asserts claims 4, 16, and 23. Claim 4 is for a chemical compound risedronate, or "a pharmaceutically acceptable salt or ester thereof." Claim 16 is for a pharmaceutical composition containing risedronate. Finally, claim 23 defines a method of treatment of "diseases associated with abnormal calcium and phosphate metabolism" by administering a "safe and effective amount" of a pharmaceutical composition comprising risedronate. It is undisputed that osteoporosis, the disease whose treatment is claimed in claim 14 of the '406 patent, is a disease involving abnormal calcium and phosphate metabolism. (JTX1, col.1, ll.24-40.) The '122 patent specification defines "safe and effective" in terms of dosage ranges:

> However, single dosages can ranges from about 0.001 mg P to about 3500 mg P, or from about 0.1 micrograms P/kg of body weight to about 500 mg P/kg of body weight. Preferred single dosages are from about 0.1 mg P to about 600 mg P, or from about 0.01 to about 50 mg P/kg of body weight.

(JTX1, col.12, ll.21-26.) The dosage range specified in claim 15 of the '406 patent (0.00025 mg P/kg to 0.01 mg P/kg) is fully encompassed by the "safe and effective" range of claim 23 of the '122 patent. (Lenz 118-19.)

C. The Claimed Invention of the '122 Patent Would Have Been Obvious in View of the Invention of Claim 15 of the '406 Patent

The essential difference between claim 15 of the '406 patent and claim 4 of the '122 patent is that the latter is specific to risedronate rather than describing the use of 2-pyr EHDP, its isomer. The inquiry, then, is whether risedronate would have been obvious in light of 2-pyr EHDP. The obviousness of a chemical compound analytically involves answering two questions. First, is the new compound, here risedronate, prima facie obvious in view of the prior compound, here, 2-pyr EHDP? If the answer is yes, then the question becomes whether the patentee can demonstrate that the new compound possesses some unexpected beneficial property compared to the old compound. If the patentee cannot do so, then the compound is unpatentable and a claim to it is invalid. *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (en banc).

1. Risedronate is Prima facie Obvious in view of Claim 15 of the '406 Patent

In cases involving the obviousness of chemical compounds, a prima facie case of obviousness is made by a showing of "structural similarity between the claimed subject matter and the prior art subject matter … where the prior art gives reason or motivation to make the claimed compositions." *Dillon*, 919 F.2d at 692. Here, the structures of 2-pyr EHDP and risedronate are as close as they can be without being identical, and although in the double patenting context the "motivation" factor is not pertinent, *Geneva*, *supra*, the prior art certainly supplied the motivation to make risedronate in any event.

(a) A Person of Ordinary Skill Would Have Been Motivated to Make Risedronate

A person of ordinary skill in the art who was aware of claim 15 of the '406 patent would have been motivated to move the position of the nitrogen on the pyridine ring on

2-pyr EHDP to make risedronate, with a reasonable expectation that the resulting compound would have activity useful in treating diseases involving calcium and phosphate metabolism. Based on claim 15 of the '406 patent a person of ordinary skill in the art would have understood 2-pyr EHDP to be safe and effective for the treatment of osteoporosis, a bone disease. That person would also have understood 2-pyr EHDP to be the most potent of any of the compounds listed in claim 15, since that claim associates it with a much lower dosage range than any of the other compounds. (Lenz 88-90; McKenna 682-84.) Thus, one of ordinary skill in the art had ample motivation to choose 2-pyr-EHDP as the compound to start with, that is, to employ it as a "lead compound," and to modify it to obtain additional compounds useful in the treatment of diseases involving calcium and phosphate metabolism disorders.

A person skilled in the art who was aware of the potent bone resorption inhibition activity of 2-pyr EHDP would have been motivated to make the other two positional isomers (risedronate and 4-pyr EHDP). This motivation would have arisen both because of a belief that risedronate would have similar activity and in order to study the structure-activity relationship among the three isomers. (Lenz 96-98). That persons skilled in the art of medicinal chemistry were motivated to make all three positional isomers of pyridine-containing compounds is demonstrated by the fact that those who actually discovered commercial drug substances routinely made this type of modification. For example, the developers of the following drugs, all of which were commercial products,

disclosed the conception, making and/or testing of two or more of the possible positional isomers of pyridine-containing compounds:

Drug	Patent or Literature Reference	DTX	No. Isomers Disclosed or Tested
Milrinone	USP 4,004,012	45	All three
Amrinone	USP 4,072,746	43	All three
Zimelidine	USP 3,928,369	46	All three
Propiram	USP 3,163,654	49	All three
Diisopyramid	USP 3,225,054	48	All three
Pinacidil	USP 4,057,636	44	Two
Piroxicam	USP 3,591,584	47	All three (one in the patent, the other two in other literature)
Aza-Fentanyl	Analogs Arch. Pharm. 311.1010 (1979)	52	All three

(DTX310; Lenz 98-105).

In addition, both Dr. Benedict and Dr. Lenz, Teva's expert, both of whom were researchers in the field of medicinal chemistry at the time of the invention, followed this methodology. In fact, Dr. Benedict followed this methodology to arrive at the claimed invention. First, he synthesized 2-pyr EHDP by a difficult synthetic method. Then, he found a "one-pot" synthesis in the patent literature, and immediately synthesized all three isomers by using readily available starting materials. (DTX150 at PG45560; Benedict 109-11; McKenna 679.) Dr. Lenz took this same approach during his own research. In the mid 1980's he purchased the same starting materials Dr. Benedict used to make the three isomers of risedronate to make all three positional isomers of certain pyridine-

containing compounds he was studying because he was motivated to study the properties of each. (Lenz 111-12.)

Dr. McKenna testified that he found examples in the literature in which chemists had apparently made one pyridine isomer but not "both" of the others (he did not say how many were made). However, he was neither able to identify the compounds he was referring to, nor could he explain how he conducted his search of the literature. (McKenna 628.) Dr. McKenna's observation is therefore not probative on the issue whether persons skilled in the art would have had the motivation to make other isomers of pyridine-containing compounds.

Not only would one of ordinary skill in the art be motivated to make the positional isomers of 2-pyr-EHDP, but by mid-1985, the technical literature disclosed how to synthesize 2-pyr EHDP and its positional isomers. For example, a synthesis for making aminobisphosphonates was disclosed in UK Patent Application No. 2,118042 A, which covered alendronate. This synthesis could be adapted to make 2-pyr EHDP and its positional isomers by changing the starting materials used to attach the R_2 group to the bisphosphonate head. In particular, instead of using aminobutyric acid, one of ordinary skill in the art could use 2-pyridyl acetic acid, 3-pyridyl acetic acid or 4-pyridyl acetic acid, depending upon which isomer was being synthesized. This is the same synthesis that was disclosed in the '122 patent for making 2-pyr EHDP. As evidenced by Dr. Benedict's and Dr. Lenz's experience, the starting materials for making each of the isomers were commercially available from the Aldrich catalogue at the time. (Lenz 111.)

(b) The Person Skilled in the Art Would Have Had a Reasonable Expectation of Success

2-pyr EHDP and risedronate differ in only one respect: the position of the substitution on the pyridine ring (the 2- position vs. the 3-position). The molecules have the same number of carbon, nitrogen, oxygen and hydrogen atoms. They have the same molecular weight. (DTX307; Lenz 92-93; McKenna 659-60.) 2-pyr EHDP and risedronate are not "chiral" compounds; neither exists in the form of enantiomers, and they are not enantiomers of each other. (McKenna 674; Lenz 280-82.) Both 2-pyr EHDP and risedronate exist as crystalline solids at room temperature. (McKenna 660; JTX1, col.8, ll.34-35.)

In the mid-1980s, persons skilled in the art knew that bisphosphonates as a class of compounds inhibited bone resorption. In addition, persons skilled in the art were aware that the addition of the hydroxy (–OH) group to the head of the bisphosphonate molecule would enhance bone resorption inhibition activity. (PTX355 at PG191240-41; McKenna 667, 670-71; Lenz 71, 107-08.) In the mid-1980s, persons skilled in the art were aware that adding of a nitrogen-containing substituent to the bisphosphonate tended to enhance bone resorption inhibition activity. (Lenz 71, 107-108; McKenna 667, 669-71.) 2-pyr EHDP is a bisphosphonate, it has a hydroxy group incorporated into the head portion of the molecule, and a nitrogen-containing substituent on the tail portion of the molecule. (Lenz 91-93; McKenna 658-60.) Risedronate is a bisphosphonate, it has a hydroxy group incorporated into the head portion of the molecule, and a nitrogen-containing substituent on the tail portion of the molecule. (Lenz 74-75; McKenna 658-60.) Because of the close structural similarity between 2-pyr EHDP and risedronate, and because risedronate is a bisphosphonate, includes a hydroxy group in the head portion,

and a nitrogen-containing substituent on the tail portion, a person skilled in the art who was aware of the activity of 2-pyr EHDP would have reasonably expected risedronate likewise to have bone resorption inhibition activity. (Lenz 92-93, 104-107.)

In fact, Dr. Benedict testified that he expected bisphosphonate compounds with similar structures to exhibit similar properties, including bisphosphonates that differed in exactly the manner in which 2-pyr EHDP and risedronate differ: the 2- vs. the 3- position on a pyridine ring. (Benedict 498.)

P&G argues that the bisphosphonate art was so unpredictable that one of ordinary skill in the art could have no expectations at all. P&G relies primarily on out-of-context snippets from the contemporaneous publications of Dr. Herbert Fleisch, one of the leaders in early bisphosphonate study. A closer analysis of Dr. Fleisch's work, however, belies the inferences P&G seeks to draw. First, as Dr. McKenna, P&G's expert conceded, Dr. Fleisch confirmed that by 1985 it was known that bisphosphonates as a class were useful in inhibiting bone resorption. (PTX355 at PG191240-41; McKenna 669.) Dr. McKenna agreed that Dr. Fleisch taught that a hydroxyl (–OH) group attached to the geminal carbon enhanced the potency of the molecule and, in fact the hydoxybisphosphonate was established as the most effective head group. Dr. McKenna also agreed that this teaching was a structure-activity relationship. Dr. Fleisch also pointed out that incorporating a nitrogen atom onto the tail group could greatly increase the bone resorption inhibiting properties of a bisphosphonate, yet another structure-activity relationship. (PTX355 at PG191241; McKenna 670.) In fact, despite P&G's assertions of "unpredictability," no P&G witness identified a single bishphosphonate that did not exhibit at least some bone resorption activity.

Both compounds at issue in this case are bisphosphonates, a class of compounds taught by Dr. Fleisch be active in inhibiting bone resorption. They are both hydroxybisphosphonates, predicted by Dr. Fleisch to be have enhanced activity, and both incorporate a nitrogen atom in the tail group, another feature identified by Dr. Fleisch as enhancing activity. Thus, based on the known structure activity relationships alone the skilled person would have an expectation that both compounds would be highly active in inhibiting bone resorption.

The case law is replete with examples of compounds found prima facie obvious in view of closely related compounds. Indeed, structural similarity by itself may be sufficient to establish prima facie obviousness. *In re Payne*, 606 F.2d 303, 313-14 (C.C.P.A. 1979). This closeness in structure is most apparent in the case of isomers, and many decisions have found compounds prima facie obvious over prior art isomers. In *In re Norris*, 179 F.2d 970, 973-74 (C.C.P.A. 1950), the claimed compound was useful as an intermediate for production of keto nitriles and esters, and was held to be prima facie obvious over prior art disclosing its isomer because it possessed no utility above and beyond what was expected. In *In re Mayne* 104 F.3d 1339, 1343 (Fed. Cir. 1997), the applicant claimed certain protein compounds that differed from the prior art proteins by only an amino acid in the sequence. In the prior art, the amino acid was leucine, but in the claimed proteins leucine was replaced by its isomer isoleucine. Leucine and isoleucine are positional isomers – they differ from each other only in the position of a carbon atom – and have similar chemical and physical characteristics. The prior art also suggested that they could be used for the same purpose. The court therefore found that the claimed protein was prima facie obvious. *See also In re Mageli*, 470 F.2d 1380

(C.C.P.A. 1973) (claimed polymerization inhibitor was an isomer of a prior art compound, also a polymerization inhibitor); *In re Jones*, 162 F.2d 638, 640 (C.C.P.A. 1947) (claimed compound prima facie obvious from prior art disclosure of isomer having same utility); *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 370 (D. Del. 1991) (pharmaceutical compound prima facie obvious in view of its isomer).

Although structural similarity may be sufficient to show prima facie obviousness, as discussed above, the record contains much more evidence, including the motivation to make risedronate, and the expectation that risedronate would be active in inhibiting bone resorption. This additional evidence makes the prima facie case even stronger. *Danbury*, *supra*; *In re Merck & Co.*, 800 F.2d 1091, 1096-97 (Fed. Cir. 1986) (conclusion of prima facie obviousness supported by evidence of motivation and practice in the art)

2. Risedronate Does Not Exhibit any Unexpected Results Compared to 2-pyr EHDP

Recognizing that the virtual identity between 2-pyr EHDP and risedronate was sufficient to demonstrate the prima facie obviousness of risedronate, P&G attempted to rely on alleged unexpected results. P&G presented data on the activity of the two compounds in animal models, and on toxicity data it obtained from screening tests conducted at the time the compounds were first examined. Neither the activity data nor the toxicity screens establish any differences between the two compounds, much less any "unexpected" differences sufficient to make risedronate patentable over 2-pyr EHDP.

Indeed, with respect to the "degree" of unexpected results required to defeat prima facie obviousness, examples in the case law confirm that risedronate does not exhibit the unexpected properties necessary to sustain its patentability. Patentable unexpectedness means more than a mere difference; it means a substantial and significant

improvement. *See In re Hoch*, 428 F.2d 1341, 1344 (CCPA 1970) ("substantial, actual differences in properties" required); *In re Merck & Co.*, 800 F.2d at 1098-99 (prima facie obviousness not overcome because "alleged difference in properties….is a matter of degree rather than kind"); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1481 (Fed. Cir. 1997) (statistically significant variation from expected result not sufficient to overcome prima facie showing of obviousness); *Monsanto Co. v. Rohm & Haas Co.*, 312 F. Supp. 778 (M.D. Pa. 1970) (difference in properties between patented compound and prior art compound only "one of degree"); *Danbury*, 777 F. Supp. at 365 (D. Del. 1991):

> [A]ny differences exhibited between the various beta-blocker drugs are a matter of degree. Some of the studies cited by ICI may indicate that [the patented drug] has less of a particular effect as compared to certain other beta-blocker drugs in some patients, but in the Court's view, the evidence was not sufficient to find that [the patented drug] possesses an unexpected degree of superiority as compared to the prior art beta-blockers with respect to side effects.

P&G's test data show nothing that could be characterized as a difference, much less a "difference in kind," between 2-pyr EHDP and risedronate.

(a) P&G's Activity Testing Shows that Risedronate Does Not Exhibit any Unexpected Potency Advantage over 2-pyr EHDP

(i) P&G's Lowest Effective Dose Data Do Not Establish Superiority Because P&G Never Determined the LED for Both Compounds in the Same Test

During the mid-1980s, P&G employed two animal tests to screen compounds for inhibition of bone resorption activity: the TPTX test and the Schenk test. (Miller 840-41.) In the TPTX test, the test animals (rats) are treated surgically to remove their thyroid and parathyroid glands. (Miller 845-46.) The latter gland secretes a hormone that regulates calcium metabolism, including bone resorption. The rats are then fed a low

calcium diet. (*Id.* at 847.) After the calcium blood level has become minimized, the animals are administered the test drug for several days, followed by a dose of parathyroid hormone. The hormone stimulates bone resorption, increasing the blood calcium level. The blood calcium level is measured, and if the test compound is active to inhibit bone resorption, the level will be lower than for the control. (P038). For many compounds, P&G carried out this test on several different groups of rats, each one receiving a different dose. The lowest dose at which activity was observed was called the "lowest effective dose," or "LED" for the compound. (Lenz 131-32).

In addition to the TPTX test, P&G employed the Schenk test. In this method, young growing rats are injected with a compound that "marks" the bones so that the experimenter later examining the bones can determine the beginning of the experiment. (Lenz 132-33.) The rats are administered the test compound for several (typically seven) consecutive days. (Miller 849.) One group of rats is not administered the test compound, and acts as a control group. At the end of the test period, the animals are killed and the tibias are dissected and observed.

At P&G, the earlier analyses of the tibia were performed by a histological method; that is, the dissected bone was examined microscopically and the percent trabecular bone was determined. The percent trabecular bone in the control group was subtracted from that number. The greater this difference, the more active the test compound was at inhibiting bone resorption. (McOsker 716-17). As with the TPTX test, P&G often carried out the Schenk test using different doses on different groups of rats. The lowest dose at which a compound yielded a statistically significant difference in

percent trabecular bone with respect to the control group was reported as the LED. (Miller 844.)

In 1985 P&G submitted a sample of 2-pyr EHDP for testing for potency using the TPTX test at the University of Arizona. The test was carried out at 1.0, 0.1, 0.01, and 0.001 mg P/kg. The compound was active at the lowest level tested. (DTX313.) In 1985 P&G submitted a sample of risedronate for testing for potency using the TPTX method at the University of Arizona. The test was carried out at 1.0, 0.1 and 0.01 mg P/kg. The compound was active at the lowest level tested. (PTX139.) In September 1985, P&G tested risedronate using the TPTX method carried out at P&G's facilities. The test was carried out at dosage strengths of 0.1 mg P/kg, 0.01 mg P/kg, 0.001 mg P/kg and 0.0003 mg P/kg. (PTX 514.) The compound was active at all doses. (PTX22.)

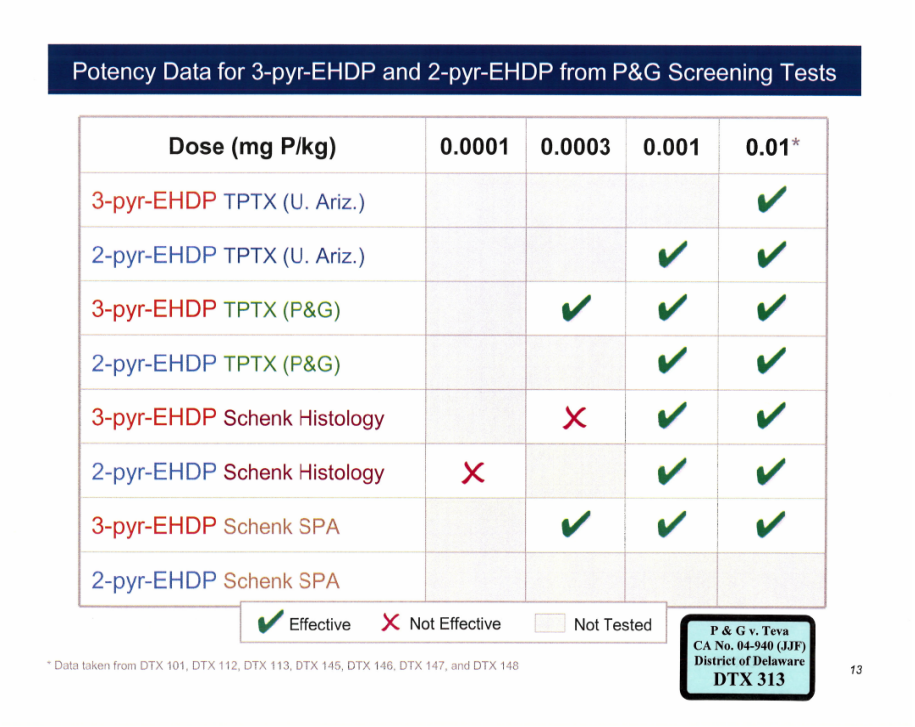
In March, 1985, P&G tested 2-pyr EHDP using the TPTX method carried out at P&G's facilities. The test was carried out at dosage strengths of 1.0, 0.1, 0.01 and 0.001 mg P/kg. The compound was active at all doses. (PTX516.) However, P&G did not test 2-pyr EHDP at 0.0003 mg P/kg, the lowest dose at which it had tested risedronate. It is therefore not possible to determine whether 2-pyr EHDP is more potent, less potent or has the same potency as risedronate in that test. (Lenz 136-37; McOsker 757-58.)

In May 1985, P&G tested 2-pyr EHDP using the Schenk model using the histological method of analysis. The test was performed at doses of 10.0, 1.0, 0.1, 0.01, 0.001 and .0001 mg P/kg. The compound was active at 0.001 mgP/kg. (PTX518.) 2-pyr EHDP was not found active using the histological method of analysis at 0.0001 mg P/kg, and was not tested at the three times higher dose of 0.0003 mg P/kg. (PTX518 at PG191446.) In August 1986, P&G tested risedronate using the Schenk model using the

histological method of analysis. The test was performed at doses of 1.0 mg P/kg, 0.01 mg P/kg, 0.001 mg P/kg and 0.0003 mg P/kg. At the time, P&G scientists reported that the test results showed that the compound was active at all doses except 0.0003 mg P/kg. At that dose the parameter used to measure activity (percent trabecular bone compared to control) was not statistically significantly different from zero. (PTX22 at PG23097, PG23101; PTX519; Miller 882-83.) Since the 2-pyr EHDP was not tested at 0.0003 mg P/kg, and the 3-pyr EHDP was not tested at 0.0001 mg P/kg it is not possible to determine whether it is more potent, less potent or has the same potency as risedronate in the Schenk test using the histological method of analysis. (Lenz 137-38; Miller 909-11; McOsker 757-58.)

P&G also used another technique to analyze the amount of inhibition of bone resorption in the Schenk test. This method was called single photon absorptiometry analysis, or "SPA." (McOsker 717.) This method was generally more sensitive than the histological method, in that it would indicate bone resorption inhibition activity for a test compound at a lower dose than would be determined by the histological method. (PTX22 at PG 23097-98.) Using this more sensitive method, P&G concluded that risedronate was active at 0.0003 mg P/kg. However, P&G never tested 2-pyr EHDP using the SPA method, so that it is not possible to determine whether that method would have shown the 2-pyr EHDP was more potent, less potent or exhibited equivalent potency compared to risedronate. (McOsker 754.)

P&G's activity screening tests of 2-pyr EHDP and risedronate are summarized in the chart below. This data shows that no test was ever conducted at P&G from which any conclusion can be drawn as to which compound had the lowest LED.



Potency Data for 3-pyr-EHDP and 2-pyr-EHDP from P&G Screening Tests

Dose (mg P/kg)	0.0001	0.0003	0.001	0.01*
3-pyr-EHDP TPTX (U. Ariz.)				✔
2-pyr-EHDP TPTX (U. Ariz.)			✔	✔
3-pyr-EHDP TPTX (P&G)		✔	✔	✔
2-pyr-EHDP TPTX (P&G)			✔	✔
3-pyr-EHDP Schenk Histology		✘	✔	✔
2-pyr-EHDP Schenk Histology	✘		✔	✔
3-pyr-EHDP Schenk SPA		✔	✔	✔
2-pyr-EHDP Schenk SPA				

✔ Effective ✘ Not Effective Not Tested

* Data taken from DTX 101, DTX 112, DTX 113, DTX 145, DTX 146, DTX 147, and DTX 148

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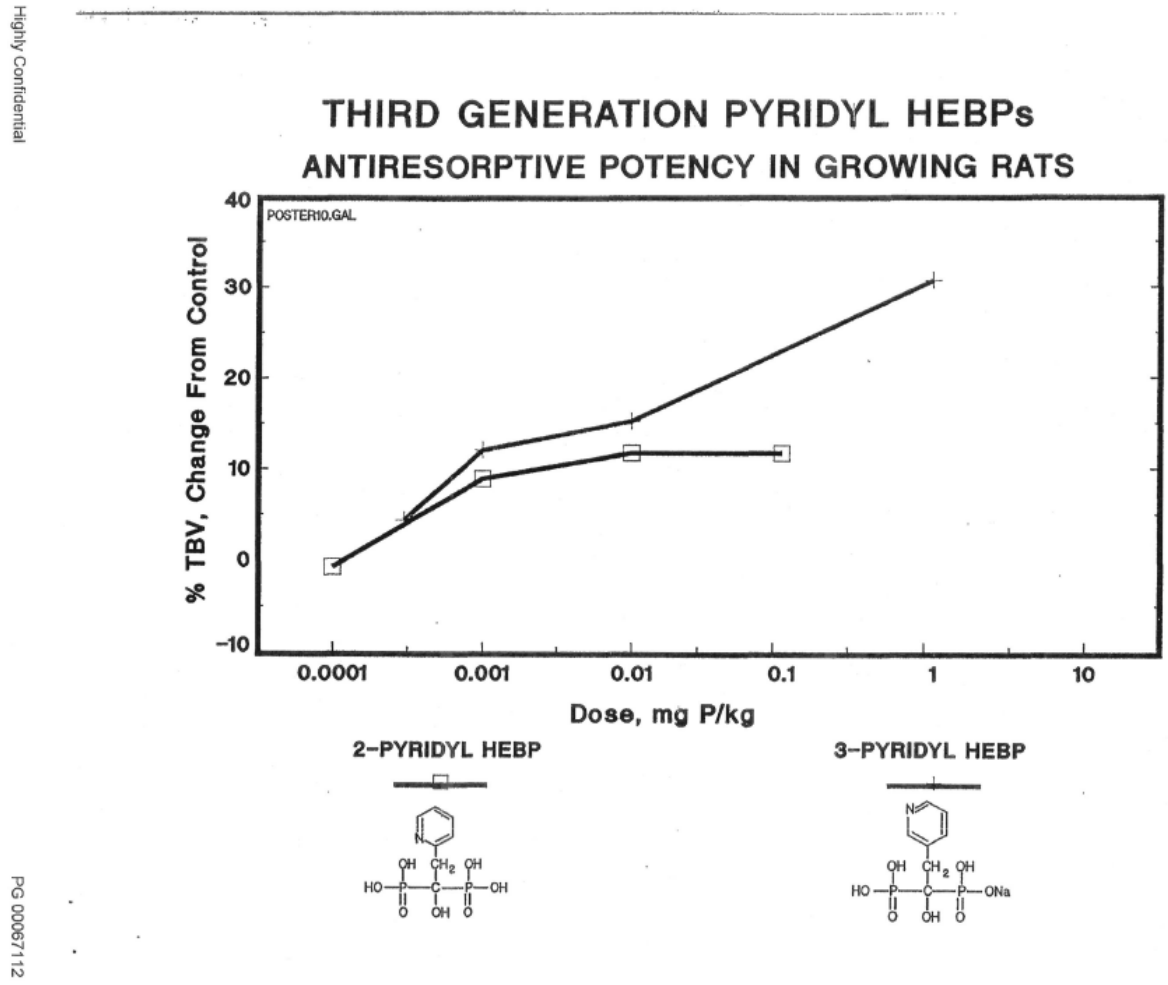
(ii) P&G's Comparison of Schenk Data for 2-pyr EHDP and Risedronate Does Not Establish Superiority

In 1988, P&G scientists submitted a manuscript for publication (DTX144), which included data from the Schenk histological analysis for 2-pyr EHDP and risedronate. The data for each dosage strength were obtained by subtracting the percent trabecular bone for each dose from the control for the experiment. (Lenz 141). Thus, the data show not only whether the compound was active at the particular dose, but also quantify that activity. The plotted data, as drawn by P&G's scientists at the time, show that at low doses, 2-pyr EHDP and risedronate are indistinguishable from each other in terms of activity. (Lenz 142-43; DTX144 at PG67112). The published version of the article does not include the graphical presentation, but does include the same data in tabular form.

(DTX74; Miller 945). The figure as plotted by P&G scientists and submitted for publication in 1988 is shown below.



(DTX144 at PG67112.)

At trial, P&G's litigation expert, Dr. Miller, recalculated the Schenk histological data for 2-pyr EHDP and risedronate differently from the manner in which P&G had done so before this litigation. This recalculation makes the differences between 2-pyr EHDP and risedronate appear larger than they do in P&G's pre-litigation presentation of the data. (Miller 875-77.) Dr. Miller did not provide a cogent explanation for not using

the pre-litigation methods that P&G used internally and published in the scientific literature. (Miller 875-82.)

Even using Dr. Miller's methodology, however, there is no significant difference in activity between the two compounds at any therapeutically relevant dose. In particular, the daily therapeutic dose of risedronate of five milligrams corresponds to 0.000125 mg P/kg for a 60 kg (132 lb) human patient (Lenz 143-44; Miller 911-14), and at that level, the activity of the two compounds cannot be distinguished from each other, even when the data are presented as Dr. Miller did. (Lenz 144-45; Miller 916.)

In the experiments that yielded the data on which Dr. Miller relied, 2-pyr EHDP activity was measured at 0.1 mg P/kg, 0.01 mg P/kg and 0.001 mg P/kg. Risedronate activity was measured at 1.0 mg P/kg, 0.01 mg P/kg, 0.001 mg P/kg and 0.0003 mg P/kg. Thus, the only dosage strengths at which both were measured were 0.01 mg P/kg and 0.001 mg P/kg. The laboratory records, however, show that for the risedronate the test animals mistakenly received a 100-fold excess dose during the 0.01 mg P/kg experiment, which biased that experiment. (PTX519 at PG191472; Miller 897-99). Accordingly, there is only a single data point, 0.001 mg P/kg, at which a comparison of any sort can be made, and at this point the difference was small according to P&G's method of comparison. (DTX74 at 396, Table VI (12.1 percent for risedronate, 8.9 percent for 2-pyr EHDP)).

(iii) Later Data Suggest that 2-pyr EHDP Might Actually Be More Active than Risedronate

In 1998, several scientists, including P&G internal expert Dr. Ebetino, published a paper in *Bone*, a refereed journal of which Dr. Miller, one of P&G's experts, is an editor. (DTX36). In that paper, they reported on bisphosphonate bone resorption inhibition

activity for several compounds, including 2-pyr EHDP and risedronate. The test they used, however, was different from both the Schenk test and the TPTX test. In this test, 2-pyr EHDP was almost three times as active as risedronate. (Lenz 148; DTX36 at 440). In discussing these results, the authors concluded that the potency of 2-pyr EHDP was essentially equivalent to that of risedronate:

> Replacement of the nitrogen functionality in a different position in the ring structure ([2-pyr EHDP]). . . did not alter the potency of these compounds relative to risedronate.

(Lenz 148; DTX36 at 441.)

(iv) The ’122 Patent Does Not Distinguish between 2-pyr EHDP and Risedronate in Terms of Activity

The ’122 patent claims both 2-pyr EHDP and risedronate. It includes several examples, and discusses both compounds. Example I of the ’122 patent describes an oral dosing regimen for treating osteoporosis using a specific pharmaceutical composition. It states that “[s]imilar results are obtained when” the named bisphosphonate “is replaced with” a compound from a list of 15 bisphosphonates. That list includes both 2-pyr EHDP and 3-pyr EHDP. (JTX1 at 9:35-65.) Similarly, Example II of the ’122 patent describes an oral dosing regimen for treating osteoporosis using a specific pharmaceutical composition. It states that “[s]imilar results are obtained when” the named bisphosphonate “is replaced with” a compound from a list of 15 bisphosphonates, which includes both 2-pyr EHDP and 3-pyr EHDP. (JTX1 at 10:1-30.) In Example III, the patent includes the same teaching for an injectable dosing regimen for treating hypercalcemia of malignancy using a specific pharmaceutical composition. (JTX1 at 10:35-60.) Example IV also describes an injectable dosing regimen for treating hypercalcemia of malignancy and includes the same observation. (JTX1 at 16:55-17:15.)

Thus, when claiming both compounds in its patent, P&G recognized that both were active, and that neither had a significant advantage over the other.

To summarize the activity data, in the TPTX test, there is no evidence that risedronate is any more or less active than 2-pyr EHDP. For the Schenk test, the evidence shows that the difference, if any, is slight and not meaningful at therapeutic levels. For the 1998 test, P&G's own data, published in a refereed journal, indicate that 2-pyr EHDP is actually more active than risedronate by a factor of three.

Having selected one of the two compounds for development, P&G now attempts to extend its patent protection for it by touting its alleged unobviousness over the other. In doing so, it contradicts its *ante litam motam* views, selectively presents its data to ignore that data which is inconvenient, and grossly exaggerates the significance of what it has selected. The data do not lie; they show that with respect to activity, both 2-pyr EHDP and risedronate are highly active. The latter, however, is not unexpectedly more active, or even more active at all, than the former.

(b) Risedronate Does Not Exhibit an Unexpected Toxicity Advantage Compared to 2-pyr EHDP

In addition to potency, P&G relies on a claim that risedronate is unexpectedly less toxic than 2-pyr EHDP. P&G's allegation, based on the scantiest of data, does not withstand analysis. Even if P&G's claim is true, however, it is meaningless in the real world. All available data shows that 2-pyr EHDP was essentially as safe as risedronate.

In connection with its work on bisphosphonate compounds, P&G developed a toxicity screening test. For each compound, a group of test animals was administered the test compound at 0.25 mg P/kg, another group at 0.75 mg P/kg and a third group at 2.5 mg P/kg. (DTX109.) Each dose was administered twice, on consecutive days. The

animals were then killed and autopsied, and visual analyses were made of internal organs, as well as chemical analyses of certain blood parameters. From this screen, P&G recorded a "no observable effects level" or "NOEL," which is the highest dose at which no toxic effects were observed. (Eastman 774-75).

For 2-pyr EHDP, P&G observed no toxic effects at 0.25 mg P/kg, but saw evidence of toxicity at 0.75 mg P/kg. P&G therefore assigned to 2-pyr EHDP a NOEL of 0.25 mg P/kg. For risedronate, P&G observed no toxicity at 0.25 mg P/kg or 0.75 mg P/kg, but saw toxic effects at 2.5 mg P/kg. P&G therefore assigned to risedronate an NOEL of 0.75 mg P/kg. (DTX109 at PG66839).

Although the NOEL for risedronate was three times that of 2-pyr EHDP, this fact does not imply that the former is three times less toxic than the latter. P&G scientists recognized that the two-day screen is not appropriate to determine relative toxicity. It is only useful to "predict unacceptably toxic drugs; to determine a valid relative ranking, chronic oral dosing studies would have to be initiated." (DTX114, PG76987.) P&G never conducted such dosing studies for 2-pyr EHDP.

In addition, since P&G did not conduct a two-day toxicology screen for 2-pyr EHDP at any dose between 0.25 and 0.75 mg P/kg, the actual NOEL cannot be determined. It could be, for example, that the true NOELs for these compounds are very similar: for 2-pyr EHDP, only slightly below 0.75 mg P/kg and for risedronate, only slightly above it. (Lenz 124-25.) Indeed, P&G's own toxicity expert, Dr. Eastman, recognized the imprecise nature of the two-day i.v. toxicology screen, and characterized the toxicities of 2-pyr EHDP and risedronate (0.25 mg P/kg and 0.75 mg P/kg) as "similar." (DTX84).

Another reason that the two-day screen represents an inadequate ranking tool is that it does not account for other important types of toxicity. In particular, P&G also carried out a test specifically designed to screen for liver toxicity.[5] In that test, 2-pyr EHDP was in fact less toxic than risedronate: the NOEL for 2-pyr EHDP was twice that of risedronate. (DTX94 at PG10755 and PG10756; Miller 925-26). Thus, as P&G's internal scientists recognized at the time, the complex question of which of two compounds is more toxic cannot be answered based on a simple two-day screen.

One way of considering toxicity is to calculate a therapeutic ratio, or safety ratio, which is defined as a toxic dose divided by the effective dose. (Miller 903; Eastman 793-94.) Thus, a drug that shows toxicity at a particular dose may still be completely acceptable if it shows efficacy at a much lower dose. (Miller 905-906.) For 2-pyr EHDP and risedronate, the data indicate that both are completely safe at any conceivable therapeutic dose. The therapeutic ratio, that is, the ratio between the high non-toxic dose (taking into account the actual amount of blood in the body) for 2-pyr EHDP, and assuming a therapeutic dose of 5 mg, is about 13,000. At the time the FDA was seeking ratios of only about 100. Both 2-pyr EHDP and risedronate are "very, very safe drugs," so that any difference between them has no practical significance. (Lenz 129.)

Data in Tables II and III of the '406 patent indicate that in the Schenk test, 2-pyr EHDP was "lethally toxic" a dose of 1.0 mg P/kg, but was effective at 0.001 mg P/kg. A therapeutic ratio defined by the lethal dose divided by the lowest effective dose is 1,000, based on the Schenk test. In that same test, alendronate was lethally toxic at a dose of 10

[5] P&G viewed liver toxicity as an important concern. At one time it considered developing 2-pyr EDP (not 2-pyr E*H*DP), but abandoned that compound in view of data showing potential liver toxicity. (Eastman 811-12.)

mg P/kg, but was effective only at 0.1 mg P/kg, which yields a therapeutic ratio of only 100, a factor of ten less favorable than for 2-pyr EHDP. Alendronate is an "outstanding" drug. (Bilezikian 406.) It is approved as "safe and effective" for treatment of bone disease. P&G's expert Dr. Bilezikian prescribes it for osteoporosis patients. (Bilezikian 383-84.) Risedronate exhibits no demonstrated toxicity advantage over alendronate. (Bilezikian 399.) In fact, Fosamax (alendronate) outsells Actonel by two-to-one, even though P&G has spent more than $1 billion marketing Actonel. (Bilezikian 405; Smith 1013-14.) Since the data in the '406 patent indicate that 2-pyr EHDP has an even more favorable therapeutic ratio than alendronate, there is no basis to conclude that risedronate has any significant safety advantage over 2-pyr EHDP.

P&G filed the application for the '122 patent six months after it filed the application for the '406 patent, which contained the data in Table III. Dr. Benedict nevertheless characterized 2-pyr EHDP as a "preferred" compound, along with risedronate. He testified that the toxicity data for 2-pyr EHDP, including P&G's NOEL data and the data in the '406 patent did not imply that the compound would not be suitable as a pharmaceutical. (Benedict 501-02).

One of the goals of bisphosphonate drug development is to find compounds that separate inhibition of bone resorption from inhibition of mineralization. (Bilezikian 375-80.) The data in Tables II and III of the '406 patent show that 2-pyr EHDP inhibits bone resorption at a very low dose (0.001 mg P/Kg), and does not inhibit mineralization at the highest dose tested. (JTX5, col.13, ll.20-39.) This property would have encouraged a person skilled in the art to pursue 2-pyr EHDP and related compounds.

P&G's chart of the therapeutic ratios calculated on the basis of NOEL divided by LED (a different basis from the ratio calculated from the data in the '406 patent), even taken at face value, shows that alendronate has a ratio similar to that of 2-pyr EHDP. In fact, both have a therapeutic ratio approximately 100 times more favorable than etidronate, even though etidronate is approved by the FDA as "safe and effective" as a treatment for bone disease. (Miller 932-33; Bilezikian 377.)

P&G has asserted that the difference in therapeutic ratios between 2-pyr EHDP and risedronate is a factor of ten. This assertion is not supported. It is based on an assumption that the LED of risedronate is 0.0003 mg P/kg and that of 2-pyr EHDP is 0.001 mg P/kg. However, 2-pyr EHDP was never tested at the 0.0003 mg P/kg level. Moreover, in a later test, using a different potency screening method, P&G showed that 2-pyr EHDP was more active than risedronate. (DTX36 at 440; Lenz 147-48.) P&G's assertion is also based on an assumption that the NOEL for risedronate is three times higher than that for 2-pyr EHDP. For the reasons discussed above, however, that assumption is also not valid.

The case law makes clear that for "unexpected properties" to trump prima facie obviousness, the properties must be truly unexpected and truly significant. Here, the property of inhibition of bone resorption would have been reasonably expected, since the compounds are so closely related and virtually all compounds in the class exhibit bone resorption inhibition activity to some degree.

3. Commercial Success is not Probative of Obviousness

Although commercial success is not relevant in the doublet patenting context, *Geneva*, *supra*, it is among the objective indicia which may be considered for a determination of obviousness. *Graham*, 383 U.S. at 17. Even if it were relevant,

however, simply reciting commercial success is not the same as proving it, and showing a "nexus" between success and the patented invention is not the same as connecting commercial success with nonobiousness.

The relevance of commercial success to the non-obviousness of a patent claim is based on the economic principle that the prospect of a financial gain creates an incentive for people to move from existing technologies to improved technologies. A financial incentive will motivate those skilled in the art to seek to make improvements to existing technologies (*i.e.*, the prior art). In appropriate circumstances, one can infer that a patented improvement would not have been obvious to the hypothetical person skilled in the art based on the fact that people who were actually in the field did not make the patented improvement despite the financial incentive to do so. (David 295.)

Underpinning this analysis is the essential assumption that the prior art was known in the relevant community, and that the relevant community was free to attempt to exploit the improved technology. (David 295-96.) If the relevant community is blocked from acting upon the prior art, then the patentee's commercial success is not probative. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (commercial success of patented once-weekly dosing regimen of alendronate not probative, since only patentee had incentive to develop invention because it held exclusive rights to the drug itself, so that "chain of inferences" applicable in instances in which commercial success *might* be utilized, failed).

As in *Merck*, the chain of inferences necessary for commercial success to be probative fails here. Here, the compound and the use of that compound against which the unobviousness of risedronate is measured was 2-pyr EHDP, which was known only

within P&G. There is no basis to assume that people in the field did not seek to make risedronate after becoming aware of 2-pyr EHDP because no one outside of P&G had knowledge of 2-pyridyl EHDP. Accordingly, all the sales of Actonel only show at most that risedronate is a good drug. However, because the prior art compound was unknown to those in the art, those sales cannot prove that risedronate would have been unobvious to them.

IV. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 103

Even if the claims are not found to be invalid for obviousness-type double patenting, they are nevertheless invalid in view of the '406 patent under 35 U.S.C. § 103, because the invention "would have been obvious to a person of ordinary skill in the art" as of mid-1985. Here, the '406 patent is statutory prior art because it is

> a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent . . .

35 U.S.C. § 102(e).

The '406 patent was filed on June 6, 1985, by Dr. Flora and Mr. Floyd, an inventive entity that is "another" with respect to Drs. Benedict and Perkins. *In re Land*, 386 F.2d 866 (C.C.P.A. 1966). The earliest application which P&G can rely upon for priority for the '122 patent was filed on December 6, 1985. Accordingly, unless P&G can show that Drs. Benedict and Perkins jointly conceived of the inventions of claims 4, 16, and 23 prior to June 6, 1985, the '406 patent is available as prior art for a 35 U.S.C. §103 obviousness analysis.[6] *Hazeltine Research, Inc. v. Brenner*, 382 U.S. 252 (1965).

[6] 35 U.S.C. § 103 was amended on November 29, 1999 to preclude reliance on 35 U.S.C. § 102(e) art where there is a common duty of assignment. However, this amendment (continued…)

In order to establish a date of invention earlier than June 6, 1985, P&G bears the burden of proving "conception" of the claimed inventions of claims 4, 16, and 23. *Chen v. Bouchard*, 347 F.3d 1299 (Fed. Cir. 2003). To establish conception, P&G must prove that Drs. Benedict and Perkins had a "definite and permanent idea" of the claimed invention. *Hitzeman v. Rutter*, 243 F.3d 1345, 1356 (Fed. Cir. 2001); *see also Bosies v. Benedict*, 27 F.3d 539, 543 (Fed. Cir. 1994) ("The question of conception is properly directed to whether there was 'formation [ ] in the mind of the *inventor* of a definite and permanent idea of the complete and operative invention . . .'") (quoting *Coleman v. Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985)) (emphasis in original).

A. P&G Failed to Demonstrate a Date of Invention prior to the Filing Date of the '406 Patent, so that the Entire Patent is Prior Art

Dr. James Benedict stated that he had made 3-pyr EHDP (risedronate) in May 1985. (Benedict 420-21.) However, Dr. Benedict did not testify about the conception of 3-pyr EHDP specifically prior to May 1985, nor about the conception of any specific dosing ranges for use with 3-pyr EHDP, nor about any specific dosing ranges of 3-pyr EHDP to treat any diseases.

Other than the oral testimony of Dr. Benedict, no other witnesses testified regarding the alleged conception or making of 3-pyr EHDP in May 1985 by Dr. Benedict or Dr. Perkins. Further, no trial or deposition testimony corroborates Dr. Benedict's oral testimony regarding a May 1985 conception or reduction to practice.

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only applies to applications filed after November 29, 1999. The application leading to the '122 patent was filed in December 1995.

At trial, P&G attempted to corroborate Dr. Benedict's testimony by relying on certain unwitnessed pages from laboratory notebooks. Dr. Benedict testified about pages 15 and 16 (PG53521-22) of a notebook (PTX67) allegedly written in May 1985, and claimed this indicated his first synthesis of 3-pyr EHDP. (Benedict 467.) This notebook was never witnessed by anyone, despite P&G's policy that required that laboratory notebooks be witnessed. (Benedict 504-05.) At the time that this notebook page was allegedly written, several P&G individuals would have understood the work set forth in the notebook, but none of them witnessed the notebook page. (Benedict 507-09.) Dr. Benedict testified further that the additional discussion on page 16 regarding samples having been sent to Arizona for testing was written at some later point, and there is no indication in the notebook when this occurred. (Benedict 509.) P&G presented no testimony or evidence indicating when, if ever, any samples related to these notebook pages were sent anywhere. Accordingly, this notation does not corroborate any information on this page.

Dr. Benedict testified that when he had completed a notebook, it was sent to a library and microfilmed, but that copies could be obtained later. (Benedict 509-10.) As to this copy of the notebook, PTX67, Dr. Benedict had no information as to where the notebook was stored, or what version was produced (*i.e.*, a copy from microfilm, or a copy that was taken from storage and kept elsewhere at P&G after being microfilmed). (Benedict 510.) Dr. Benedict also testified about pages from a second laboratory notebook, PTX70. His oral testimony was that page 93 (PG54042) also corroborated his testimony regarding conception in May of 1985. Like the pages in PTX67, however, this notebook page was not witnessed by anyone. (Benedict 510.) Moreover, he did not even

sign it, and no other witness testified about it. As to PTX70, allegedly a copy of the actual notebook, Dr. Benedict testified that the version produced was not the same as that microfilmed and stored by P&G as part of the normal archival system. (Benedict 513-15.) Even as of the time of trial, Dr. Benedict had not reviewed the entire notebook to determine what changes were made to the notebook since he had sent it for archiving. (Benedict 515.) Accordingly, PTX70, as produced by P&G was not kept in this form as part of the ordinary course of business.

No qualified witness, such as a custodian of records of P&G, testified regarding PTX67 or PTX7. No witness stated that PTX67 or PTX 70 as offered into evidence is an authentic copy of the original notebook in the form that they were kept as part of the regularly conducted business activities of P&G.

P&G provided no testimony from any other witnesses, or any other evidence, that would corroborate, or independently support, Dr. Benedict's claims of conception and reduction to practice of 3-pyr EHDP prior to June 6, 1985, the filing date of the '406 patent. Additionally, neither Dr. Benedict's testimony or these exhibits indicate that Dr. Benedict or Dr. Perkins was in possession of any salts or esters of 3-pyr EHDP, any dosing size for 3-pyr EHDP, or any method of using 3-pyr EHDP with particular dosing ranges, prior to June 6, 1985.

B. P&G Has Failed to Meet its Burden of Coming Forward With Corroborated Evidence Supporting its Claimed Date of Invention

An inventor's testimony is insufficient to prove conception or reduction to practice unless it is corroborated by independent evidence. *Chen*, 347 F.3d at 1309-10 ("It is well established that when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony.").

An inventor's notebooks or other documents authored by him are not independent evidence sufficient to corroborate the inventor's testimony. *See, e.g., Hahn,* 892 F.2d at 1032-33 ("The inventor, however, must provide independent corroborating evidence in addition to his own statements and documents."); *Chen,* 347 F.3d at 1311 (an inventor's notebook was not sufficient corroborating evidence to establish a date of invention). Regardless of what is disclosed in the notebooks, as a matter of law, if they are not witnessed they are not sufficient to corroborate a claim of a date of conception. *Stern v. Trustees of Columbia Univ.*, 434 F.3d 1375, 1378 (Fed. Cir. 2006) (affirming summary judgment of non-inventorship).

The only documents that P&G presented at trial that would ostensibly corroborate Dr. Benedict's oral testimony of a pre-June 1985 conception were unwitnessed pages from two laboratory notebooks that Dr. Benedict identified as his own. One of these sets of pages were not signed by anyone, whereas the other was only signed by Dr. Benedict. Neither notebook indicates any work by his co-inventor Dr. Perkins. These notebooks, being unwitnessed, can not as a matter of law be relied upon to corroborate Dr. Benedict's oral testimony of conception.

C. The Subject Matter of Claims 4, 16, and 23 of the '122 Patent Would Have Been Obvious in Light of the '406 Patent

For the reasons set forth above for the obviousness-type double patenting arguments, claims 4, 16, and 23 of the '122 patent claim obvious variants from the teachings of the '406 patent related to 2-pyr EHDP. As set forth in detail on an element by element basis above, the subject matter of claims 4, 16, and 23 would have been obvious in light of the teaching of 2-pyr EHDP as set forth in the claims of the '406 patent.

A consideration of the specification of the ’406 patent as a whole reinforces the conclusion based on a comparison of the claims. The ’406 patent specification includes test data not found in the claims. In particular, Table I of the specification includes TPTX data that shows that 2-pyr EHDP is active at a 10 times lower dose than alendronate, then known as the most active bisphosphonate. (Lenz 285-86; Miller 935-36.) Table II sets forth Schenk test data that demonstrates activity of 2-pyr EHDP at a 100 times lower dose than alendronate. (Lenz 285-86.) Thus, the specification teaches, even more starkly than the claims, that 2-pyr EHDP is the most promising of all the known compounds, and provides the motivation to work with it and to expect success in doing so.

CONCLUSION

For the foregoing reasons, the Court should declare claims 4, 16 and 23 of the '122 patent invalid and enter judgment in favor of Teva USA.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on December 20, 2006, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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